REMARKS

Applicants would first like to thank the Examiner for the courtesy she extended to their attorneys, Max Bachrach and Anthony M. Insogna, during an interview held January 7, 2003.[1] The amendments and remarks provided herein are made further to that interview.

New claims 170-179 are pending in this application. Claims 1-169 have been canceled without prejudice to Applicants' reserve the right to pursue all of the canceled claims in one or more continuation, divisional or continuation-in-part applications. New claims 170-179 are supported by the application as filed. For example, support for the particular analysis step recited by new claims 173, 175 and 176 can be found in Section 6.4 of the specification, beginning on page 47. No new matter has been added.

A. The Invention

As discussed during the January 7, 2003 interview, the invention to which this application is directed provides high-throughput methods by which multiple solid forms (*e.g.*, polymorphs, salts and co-crystals) of small molecule pharmaceuticals can be rapidly prepared and characterized. Prior to this invention, solid forms of pharmaceuticals were not discovered rapidly or in a high-throughput fashion, but were instead often discovered by chance after significant time and effort had already been expended in bringing the pharmaceuticals to market.

For example, during the development and initial manufacture of the ritonavir, a HIV protease inhibitor sold under the tradename NORVIR®, only one crystal form of the compound was known. Bauer, J., *et al.*, *Pharm. Res.*, 18(6):859-866 (2001). Because ritonavir is not bioavailable in that form, however, the initially marketed oral formulations of the drug were capsules that contained ritonavir dissolved in a semi-solid, waxy matrix. About two years after the initial marketing of NORVIR®, various lots of the dosage form failed the dissolution profile mandated by the FDA. The failure was found to have resulted from the formation of a previously unknown polymorph of ritonavir, which was supersaturated in the solution used in the dosage form, even though the originally known polymorph was not. *Id.* This occurrence prevented the further manufacture of the original NORVIR® formulation, and seriously threatened the supply of the drug. *Id.* At some considerable cost, a new formulation was eventually developed.

[1] Applicants also thank the Examiner for informing their attorney, Max Bachrach, that the references discussed in paragraph 10 of the Office Action were located.

Problems such as those experienced with NORVIR® can be avoided using methods of this invention. This is because the methods can be used to rapidly and systematically identify a wide variety of solid forms of small molecule pharmaceuticals. Moreover, because the claimed methods allow the rapid formation and detection of different solid forms using very small amounts of pharmaceuticals (*e.g.*, less than about 100 micrograms), they can be used to obtain enormous quantities of data for even those pharmaceuticals that are very expensive and difficult to obtain. In one embodiment particularly relevant to the NORVIR® incident, the invention provides a high-throughput method of determining the effect of particular compounds on the inhibition of crystalline forms of small molecule pharmaceuticals.

The invention also provides methods that can be used to rapidly and systematically identify co-crystals of small molecule pharmaceuticals. Applicants are unaware of any prior attempts to provide anything that remotely resembles the presently claimed methods. Yet the manufacture and formation of co-crystals is becoming more and more important to the pharmaceutical industry. Their importance is due not only to the advantages crystal forms can offer to the formulation, stability and bioavailability of drugs, but also to the fact that a large number of prescription and over-the-counter pharmaceutical formulations contain two or more active ingredients. It is believed that the ability of methods of this invention to rapidly identify co-crystals of such active ingredients will revolutionize pharmaceutical research and development.

B. The Rejections Under 35 U.S.C. § 102 Have Been Obviated

On page 5 of the Office Action, claims 39-41, 43-46, 48-52 and 55 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by United States patent no. 6,267,935 to Hol *et al.* ("Hol"). Although the rejection is obviated by the cancellation of those claims, Applicants respectfully submit that none of them are anticipated by Hol. Applicants further submit that none of the claims now pending in this application are anticipated by Hol.

As the Examiner is aware, a prior art reference must disclose all the limitations of a claim in order to anticipate the invention it recites. *Manual of Patent Examining Procedure* § 2131 (8th ed., August 2001) ("MPEP"). There must be no difference between the claimed invention and the reference disclosure as viewed by one of ordinary skill in the art. *Scripps Clinic & Research Fdn. v. Genentech*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). Put another way, "[a] claim is anticipated and therefore invalid only when a single prior art reference

discloses each and every limitation of the claim." *Glaxo Inc. v. Novapharm Ltd.*, 52 F.3d 1043, 1047, cert. denied, 116 S. Ct. 516 (1995) (citations omitted) (emphasis added).

Hol does not disclose every limitation of each of the now pending claims. For example, Hol does not disclose a method of identifying crystalline polymorphs of a small molecule pharmaceutical as recited by claim 170, wherein an array is processed to provide two different polymorphs of a small molecule. Hol simply provides various solutions that can allegedly be used to crystallize macromolecules, such as proteins. *See, e.g.*, Hol, col. 1, line 65 - col. 3, line 12. Hol further does not suggest a method wherein spectroscopy such as Raman spectroscopy is used to detect polymorphs of small molecule pharmaceuticals, as recited by new claims 170 and 177. Similarly, Hol does not disclose the method of identifying crystalline polymorphs of small molecule pharmaceuticals recited by new claim 173, wherein a filtering means is used to reduce the number of processed samples in an array and similar polymorphs are grouped together.

The other claims now pending in this application are also not anticipated by Hol. In particular, Hol does not disclose a method of identifying a salt form of a compound, much less the methods recited by claims 171 and 175.[2] Hol also does not disclose a method of identifying co-crystals of small molecule pharmaceuticals, much less the methods recited by claims 172 and 176. The method of identifying compounds that inhibit crystallization which is recited by claim 174 is also not disclosed by Hol. Therefore, each of the claims pending in this application are novel over Hol.

On page 6 of the Office Action, claims 39, 43-46 and 48-56 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Otsuka *et al.*, *Drug. Dev. Ind. Pharm.* 1999 ("Otsuka"). Although the rejection is obviated by the cancellation of those claims, Applicants respectfully submit that none of them are anticipated by Otsuka. Applicants further submit that none of the claims now pending in this application are anticipated by Otsuka.

Otsuka discloses the preparation of an amorphous and two crystalline forms of the compound glybuzole using conventional recrystallization techniques. Otsuka, pages 198-9. Unlike the claimed methods of this invention, which, as discussed above, provide a substantial improvement over traditional crystallization methods, Otsuka used large amounts (*e.g.*, 1 gram) of glybuzole. *Id.*, 199. For this reason alone, Otsuka does not anticipate the

[2] Claim 171 is directed to a method of identifying salts of a small molecule pharmaceutical which provides an array containing at least two different salts that are detected using spectroscopy. Claim 175 is directed to a method of identifying crystalline salts of small molecule pharmaceuticals.

methods of identifying crystalline polymorphs recited by claims 170 and 173, much less the particular methods recited by dependent claims 177-179. Otsuka also does not disclose all of the limitations of each of the methods recited by the other claims now pending in this case. Indeed, Otsuka does not disclose anything concerning the identification of salts, co-crystals or compounds that inhibit crystallization, much less the specific methods recited by pending independent claims 171, 172, and 174-176. Therefore, Applicants respectfully submit that none of the claims now pending are anticipated by Otsuka.

C. The Rejections Under 35 U.S.C. § 103 Have Been Obviated

On pages 7-8 of the Office Action, claims 39-46, 48-56, 58 and 59 are rejected under 35 U.S.C. § 103 as allegedly obvious over Hol or Otsuka in view of United States patent no. 5,985,214 to Stylli *et al.* ("Stylli"). Although the rejection is obviated by the cancellation of those claims, Applicants respectfully submit that none of them are obvious over the cited combination of references. Applicants further submit that none of the claims now pending in this application are obvious over the cited combination of references.

As the Examiner is aware, three basic criteria must be met in order to establish a case of *prima facie* obviousness: first, there must have been a motivation to combine the cited references at the time the invention was made; second, the alleged prior art must disclose or suggest all of the limitations of the claims alleged to be obvious; and third, there must have been at the time of the invention a reasonable expectation of success. MPEP §2142. Furthermore, hindsight cannot be used to reject a claim as obvious. MPEP § 2141.01. Consequently, when determining whether or not a claimed invention is obvious, one must cast her "mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Dembiczak*, 175 F.3d 994, 999 (Fed.Cir. 1999) (reversing a determination that several claims were obvious over a combination of references that disclosed all of their limitations, but which did not provide a motivation to combine those limitations).

As discussed above, neither Hol nor Otsuka disclose all of the limitations of any of the claims now pending in this application. Stylli, which is cited in the Office Action as evidence that specific numbers or amounts of compounds can be varied (page 8), does not correct that deficiency. Stylli discloses an automated system that allegedly can be used for "identifying chemicals having useful activity." Stylli, Abstract. As Stylli is focused on the discovery of compounds, it does not disclose or suggest a method of identifying crystalline

polymorphs, salts or co-crystals of a small molecule pharmaceutical, nor does it disclose or suggest a method of identifying compounds that inhibit the crystallization of a small molecule pharmaceutical. Indeed, because Stylli focuses on the discovery of compounds, rather than on the identification of solid forms of a known compound, Applicants respectfully submit that there would have been no suggestion, prior to this invention, of combining it with either Hol or Otsuka.

Even if there had been a motivation to combine the cited references, Applicants respectfully submit that the resulting combination would not have suggested to one of ordinary skill in the art any of the claimed methods. For example, the combination provides absolutely nothing that would have motivated one of ordinary skill in the art to attempt to identify crystalline polymorphs of a small molecule pharmaceutical by providing an array of samples, each of which contains less than about 100 micrograms of the pharmaceutical, process that array in a manner that yields at least two polymorphs, and analyze the processed samples using spectroscopy, as recited by claim 170. The cited references certainly provide no suggestion of such a method using Raman spectroscopy, as recited by dependent claim 177.

Similarly, the combination of cited references provides nothing that would have motivated one of ordinary skill in the art to attempt any of the methods of identifying salts, co-crystals and compounds that inhibit crystallization recited by the other pending claims. For example, the combination does not even remotely suggest methods of identifying solid forms of small molecule pharmaceuticals that use the filtering and grouping steps recited by claims 173-176. Thus, Applicants respectfully submit that none of the claims now pending in this application are obvious over the cited art.

D. Conclusion

In view of the amendments and remarks provided herein, the claims pending in this application are believed to be allowable.

No fee is believed due for this response. However, if any fees are required for the entry of this response or to avoid abandonment of this application, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

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